

Remarks

Claims 11, 15, 21-24, 26-30, and 32-35 are pending and examined in this application. With the above amendments, claims 11, 15 and 30 are amended, and claim 36 is added, to more particularly point out and distinctly claim the invention. The amendments are made without prejudice or disclaimer.

The pending claims stand rejected from the Final Office Action of April 21, 2005, as further discussed in the Advisory Action of July 8, 2005. Applicants respectfully request reconsideration and withdrawal of the current rejections based on the following remarks.

Claims 11, 15 21-24, 26-30, and 32-35 stand rejected under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement. These rejections are traversed for the following reasons.

Applicants again assert that the instant claims are fully enabled. Claims 11 and 21-24 are directed to methods of monitoring the progression of HIV infection or AIDS in a patient. The methods comprise measuring the number of pDC2 cells in a lymphoid tissue or blood sample from the patient, and comparing the measured number with a control sample from a subject or subjects free of HIV infection or AIDS, where a number pDC2 cells in the patent sample below the number in the control indicates that the HIV infection or AIDS may be progressing. Claims 15 and 26-29 are directed to methods of assessing the effectiveness of a composition in treating HIV infection or AIDS. The methods comprise measuring the number of pDC2 cells in a lymphoid tissue or blood sample from the patient, and comparing the measured number with a sample from the patient before undergoing treatment, where an increase in the number of pDC2 cells from the sample taken after treatment indicates that the composition may be effective. Claims 30 and 32-35 are directed to methods of monitoring the progression of HIV infection or AIDS in a patient. The methods comprise measuring the number of pDC2 cells in a lymphoid tissue or blood sample from the patient, and comparing the measured number with a control sample from subjects where the HIV infection or AIDS is

progressing, where a number of pDC2 cells in the patent sample above the number in the control indicates that the HIV infection or AIDS is progressing.

Each aspect of these claims are fully enabled. Measuring the number of pDC2 cells in a lymphoid tissue or blood sample can be easily done given the instant specification, by simply counting the number of CD4+, CD3- and CD11c- cells present, as discussed on page 29, line 7 of the specification. Additionally, the specification establishes a correlation between the number of pDC2 cells and the progression of AIDS or HIV infection, since the Example at pages 28-top of page 32 establishes that pDC2 cells are the natural interferon-producing cells (see in particular Table 1), and the Example at pages 32-39 establish that interferon production negatively correlates with HIV progression and positively correlates with the effectiveness of HIV treatment (as determined by CD4<sup>+</sup> cell counts). Given this data, the skilled artisan would conclude that the quantity of pDC2 cells negatively correlates with HIV progression and positively correlates with the effectiveness of HIV treatment. This correlation was confirmed in Siegal et al., 2001, AIDS 15:1603-1612, and Feldman et al., 2001, Clin. Immunol. 101:201-210, as discussed in the Amendment and Reply dated May 17, 2004.

Furthermore, it would take only routine experimentation to establish controls for any individual. Such reference ranges could be established simply by drawing blood from the appropriate population and counting pDC2 cells using, e.g., the cell sorting methods established in the instant specification. Such a determination would not be considered undue experimentation, since there is no uncertainty in the methods used to make those determinations.

The July 8, 2005 Advisory Action reiterates the concern that the decline of IFN production correlating with HIV load is a result of increasing age of the participants of the study. This concern is based on Shodell and Siegal, 2002, Scand. J. Immunol. 56:518-521, who found "significant decreases of the circulating pDC during ageing in healthy adult humans, as defined both by flow cytometry and IFN- $\alpha$  generation. However, since the decreases of IFN with aging in that study is in healthy adult humans, that reference is not relevant to the instant claims, which relate to HIV infected patients.

Applicants also respectfully disagree that the skilled artisan would believe that the decline of IFN production is an age-related artifact, because the various correlation determinations in Table 1 control for any effect due to aging. For example, the last listed correlation, "All symptomatic subjects who were suppressed" shows the same negative correlation between interferon levels (approximating pDC2 levels) and viral burden. If pDC2 levels did not correlate with viral suppression but only with aging, then there would be a positive correlation here (while still showing a negative correlation with CD4<sup>+</sup> counts) because this correlation measures the difference between interferon levels in individuals that had symptoms and later showed viral suppression. Since the viral suppression was at a later time point, the interferon levels would be expected to be lower at the later time point if those changes were due to aging and not viral load. Thus, a positive correlation would be expected in that analysis if the variation in apparent pDC2 levels were only due to age of the patient and not viral load. However, a negative correlation, similar to CD4<sup>+</sup> levels, was found.

Applicants also point to Table 2, which shows that suppression of HIV viremia positively correlates with reconstitution of interferon generation. If interferon production by pDC2 cells was only negatively influenced by age and not related to HIV viremia, the correlations in Table 2 would be negative, because that table measures changes in interferon levels after viral suppression. Since the correlations are positive in Table 2, pDC2 and interferon levels go up over time and not down. Thus, aging cannot be the cause of the positive correlation because a negative correlation would be expected if aging and not viral suppression were affecting the measured interferon levels.

It is also noted that Table 1 and Table 2 of the instant specification show a strong correlation between interferon generation and CD4<sup>+</sup> T cell counts for each condition analyzed. As shown by Shodel and Siegal, 2002, CD4<sup>+</sup> T cell levels do not go down with age, but are known to be strongly correlated with HIV viremia. If pDC2/interferon generation in those studies were influenced by age and not viremia, there would not be similar regression slopes for interferon generation and CD4<sup>+</sup> T cell counts.

The similar recovery of CD4<sup>+</sup> T cells and interferon generation with therapeutic suppression of HIV was also noted by Siegal et al., 2001, AIDS 15:1603-1612 (provided with the Amendment and Reply Under 37 C.F.R. 1.111 dated May 17, 2004 in this case). Again, if interferon levels only negatively correlated with aging and not with HIV viremia levels, the interferon levels would go down with suppression of viremia, and would not show a rise with suppression of viremia as with CD4<sup>+</sup> cells.

Regarding the assertion discussed in the July 8, 2005 Advisory Action that the specification fails to provide any correlation between the number of interferon units produced and the number of CD4<sup>+</sup> CD3<sup>-</sup> CD11c<sup>-</sup> pDC2 cells, Applicants point to Table 1, at the top of page 32 of the specification, which clearly shows that pDC2 cells are the natural interferon producing cells. It is further noted on page 29, line 7, that pDC2 cells are CD4<sup>+</sup>CD3<sup>-</sup> CD11c<sup>-</sup> cells. With those findings, the skilled artisan would understand that increases in pDC2 cells correlate with increases in interferon production.

The PTO also asserts that the specification fails to establish any correlation between the number of pDC2-interferon-producing dendritic cells and the progression of HIV infection and/or AIDS. However, the Example at page 32 *et seq.* shows precisely that. For example, Table 1 shows a negative correlation between HIV burden and interferon generation. Additionally, Table 2 shows a positive correlation between interferon generation and suppression of HIV viremia. Those correlations, along with the finding that pDC2 cells are the naturally interferon producing cells (discussed in the paragraph immediately above) establish the correlation between pDC2 cells and HIV and AIDS (measured as those with opportunistic infection [OI]). With those findings, the skilled artisan would understand that increases in pDC2 cells negatively correlate with progression of HIV and AIDS.

Applicants again note that the negative correlation between pDC2 and HIV progression and positive correlation with the effectiveness of HIV treatment is confirmed in Siegal et al., 1999, Science 284:1835-7, which demonstrates that pDC2 cells are the principal interferon producing cell; Siegal et al., 2001, AIDS 15:1603-1612, demonstrating the negative correlation between interferon production and HIV infection;

and Feldman et al., 2001, Clin. Immunol. 101:201-210, establishing that interferon production and pDC2 levels correlate with HIV infection. In the latter reference, the PTO noted in the Final Office Action dated April 21, 2005 (p. 6) that the authors identified the interferon producing cell population using different markers than the CD4+ CD3- CD11c- markers identifying pDC2 cells in the instant invention. However, Feldman et al. call those interferon producing cells pDC2 cells, and refer to Siegal et al., 1999, Science 284:1835-7 as identifying pDC2 cells.

Regarding Siegal et al., 2001, AIDS 15:1603-1612, the Final Office Action of April 21, 2005 on page 6 also states, “. . . Siegal 2001 teaches a correlation between the interferon production and HIV disease progression using non-T, HLA-DR blood mononuclear cells known as natural IFN-producing cells (NIPC), which are phenotypically distinct from pDC2 dendritic cells as claimed in the instant invention.” However, the instant specification and Siegal et al., 1999, Science 284:1835-7 establishes that the NIPC cells are pDC2 cells. See also Feldman et al., page 201 (“. . . only recently have DC subsets in peripheral blood been clearly described, thus allowing definition of the NIPC as the precursor of the type 2 dendritic cell (pDC2) . . .”).

#### Conclusion


In light of the above discussion, Applicants respectfully request withdrawal of the rejections and passage of the claims to allowance. If there are any minor matters that prevent allowance of the claims, the PTO may contact the undersigned attorney to resolve those matters.

It is believed that the enclosed check for \$905.00 to cover the fees for a three-month extension of time (\$510.00 for a small entity) and a Request for Continued Examination (\$395.00) is all that is required with this Reply and Amendment. If there are any unanticipated fees required to maintain pendency of this application, those fees can be withdrawn from Deposit Account No. 01-1785. Overpayments may be credited to Deposit Account No. 01-1785.

Respectfully submitted

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